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Research Article

Adult Renal Cell Carcinoma – Rare - Acquired Cystic Disease Associated Renal Cell Carcinoma: Review and Update

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Abstract:

For more than twenty-three years ago acquired cystic kidney disease had become increasingly recognised as a significant risk in patients who have end-stage kidney disease, especially in those patients who are maintained on chronic haemodialysis and peritoneal dialysis. A review of the global literature had suggested that nearly fifty percent (50%) of patients who have been undergoing dialysis for more than 3 years do develop kidney cystic changes. The major complications emanating from this condition include neoplasia and spontaneous kidney haemorrhage. The risk for the development of carcinoma of the kidney had been estimated to be more than 30 times higher in dialysis patients with cystic changes in comparison with in the general population. Acquired cystic kidney disease has become increasingly recognised as a significant risk in patients with end-stage renal disease, especially in those maintained on chronic haemodialysis and peritoneal dialysis. A review of the literature indicates that nearly 50% of patients on dialysis for more than 3 years develop renal cystic changes. The major complications of this condition are neoplasia and spontaneous renal haemorrhage. The risk of developing renal carcinoma has been estimated to be more than 30 times higher in dialysis patients with cystic changes than in the general population. It is important for clinicians all over the world to be aware of the possibility of patients undergoing medium to long-term dialysis developing cystic renal disease ensued by the development of malignant kidney disease. Careful surveillance of dialysis patients utilizing yearly ultrasound scan of renal tract and computed tomography would be recommended for the regular and careful follow-up assessment of patients who are undergoing medium-term to medium-term for chronic kidney disease. Various aspects related to cystic kidney disease associated malignant tumour disease has been discussed in the ensuing article to update information related to the diagnosis, management and outcome of the tumour.

keywords: acquired cystic kidney disease; dialysis; kidney tumours; cribriform architecture; microcystic architecture; calcium oxalate crystals; cd10; ae1/ae3; amacr; fish studies; molecular and cytogenetics description; genomic microarray; acquired cystic disease-associated renal cell carcinoma; renal cell carcinoma end-stage renal disease

Introduction

It has been iterated that Dunnill and associates [1] [2] were the first to report ACDK as an effect of end-stage kidney disease, generally in patients who had been undergoing haemodialysis. [3] The condition was typified 1 cm to 2-cm cysts distributed randomly throughout the cortex and medulla of the kidney. [3] It has been generally accepted that more than 3 cysts should be present or more than 25% of the kidney should be involved and a history of polycystic kidney disease should be absent. [1] [4] The incidence of ACDK in patients who have end-stage kidney disease does range from 30% to 95%. [1] [2] It has been pointed out that the duration of maintenance dialysis is the most strongly associated risk factor. [1] [2] About eight percent (8%) of the patients who have been afflicted by end-stage renal disease have ACDK at the commencement of dialysis. [1] [5] It has been iterated that pursuant to 1 year to 3 years of dialysis, 10% to 20% of patients do develop ACDK. This rate has tended to increase to 40% to 60% at 3 years to 5 years of dialysis and up to 90% after 5 years to 10 years of dialysis. [1] [4] [5] [6] It has been iterated that the main complication in ACDK is the increased risk for the development of kidney tumours, where the incidence is 12 to 18 times higher in comparison with in the general population [3] and which occurs 20 years earlier than in the general population. [7] Kidney tumours included benign and malignant neoplasms and had been reported in 20% to 33% of patients who have ACDK. Majority of the kidney tumours arising within ACDK are benign and do correspond to papillary adenomas or oncocytoma. Other tumours as well as tumorlike conditions which had been reported

do include: angiomyolipoma, papillary hyperplasia of the cyst epithelium, and atypical epithelial hyperplasia.[1] [3] [8] [9] It has been documented that Eighteen percent (18%) of the tumours arising in ACDK are renal cell carcinoma, that had been identified in about six percent (6%) of ACDK in long-term dialysis patients.[1] [2] [10] [10] Based upon documentations from several studies, tumour transformation in ACDK does occur more frequently with longer duration of haemodialysis. [1] [7] [8]

The main types of tumours, described in the literature are papillary or conventional (clear cell type) renal cell carcinoma.[1] [3] [11] The cytogenetic changes of the papillary subtype that is associated with ACDK are similar to those that are found in tumours without ACDK. Tumours in ACDK tend to be frequently multifocal in 50% of cases and they are usually less than 3 cm in diameter. [1] The frequency of bilateral tumours in ACDK is not known, in part because of sporadic case reports and small pathology reported case series. [1] [3] Rioux-Leclercq et al. [1] stated that to their knowledge, they were the third series with a bilateral tumour arising in ACDK. [6] [12]

Usually, renal cell carcinoma which had arisen within ACDK is regarded to be a tumour of low malignant potential in comparison with classic renal cell carcinoma.[1] [11] Nevertheless, Six percent (6%) to twenty-seven (27%) of renal cell carcinomas that arise from ACDK had been reported to metastasize. [1] [13]

Uncommon cases of renal cell carcinoma with a sarcomatoid component had also been described; all of the tumours had a fatal outcome, with death occurring 2 years pursuant to the kidney tumour diagnosis.[1] [14] Even though the cell of origin of ACDK and tumour transformation has remained not known, chemical analysis of cyst fluid and ultrastructural analysis had been documented to implicate the proximal tubule.[1] [4] [7]

Postulates regarding the pathogenesis of ACDK and the development of secondary tumour include in part toxins related to haemodialysis, accumulation of mutagenic or carcinogenic uremic metabolites, immunosuppression, effect of renotrophic growth factor, renal tubular obstruction emanating from interstitial fibrosis, deposition of calcium oxalate and immune complex in the tubular lumina, focal proliferation of renal tubular epithelium, and alteration in tubular basement membrane.[1] [2] [4] [15] [16]

Many authors [7] [8] had documented that several of the cysts in ACDK had been lined by hyperplastic multilayered epithelium with papillary projections from which papillary carcinoma might arise. Michaels and associates [17] had demonstrated an increased proliferative activity in both glomerular and tubular epithelium, which might explain the large variety of epithelial neoplasms observed in dialysis patients with ACDK.

Oxalosis is a characteristic feature of kidneys that have end-stage disease and had been implicated in the pathogenesis of ACDK with tumour transformation.[1] [6]

There are more than 100 cases of ACDK with tumour in the global literature, however, only one study reported had 2 cases of papillary renal cell carcinoma with extensive tumour calcium oxalate deposits in ACDK. [16]

Rioux-Leclercq and associates [1] stated that they had reported the first case of calcium oxalate crystals in a bilateral papillary renal cell carcinoma and in a conventional (clear cell type) renal cell carcinoma arising in ACDK. Rioux-Leclercq also iterated that, all the tumours in their case series had demonstrated extensive oncocytic (acidophilic) features which had been mentioned only in one preceding study. [10] Rioux-Leclercq et al. [1] furthermore made the ensuing iterations:

- In the other study which had reported renal cell carcinoma with ACDK and oxalosis, oncocytic features had not been documented. Nevertheless, the only illustration of their tumour had demonstrated oncocytic cytoplasm. [16]
- An analysis of additional cases is necessitated in order to ascertain whether oncocytic features do appear to be characteristic of renal cell carcinoma arising in ACDK.
- Calcium oxalate crystals had previously been reported in end-stage kidney disease in the walls of ACDK. [2] [8]
- Preexisting crystals might become incorporated secondarily during neoplastic transformation.
- Other types of calcifications, including psammomatous calcifications and ossification, had also been documented.
- Many authors had studied nephrocalcin, an acidic glycoprotein that inhibits growth, aggregation, and secondary nucleation of calcium oxalate monohydrate crystals. [17]
- Nephrocalcin is produced by renal proximal tubule cells but had been also localized to cells of primary renal cell carcinoma. [17]
- Consistent with finding calcium oxalate within the tumours in their study, nephrocalcin had been documented as decreased in renal cell carcinoma in patients undergoing long-term hemodialysis. [17]
- Another postulate that could explain the relation between tumour transformation as well as oxalosis is cyst and eventual tumour formation arising as a complication of tubular obstruction by calcium oxalate crystal. [2]
- This phenomenon had appeared relatively rarely within the United States of America based upon available literature and an informal survey of many leaders in urological pathology from their country who had published extensively on renal cell carcinoma 18] Nevertheless, the finding of calcium oxalate crystals in renal tumours in patients who have been undergoing long-term dialysis does not appear to be as uncommon in Japan, where renal transplantation is not common. (Toyonori Tsuzuki, written communication, 2002).
- The finding of many calcium oxalate crystals in renal cell carcinoma might be directly related to time undergoing dialysis.
- They hoped that their study would stimulate additional information on this topic from their country and other countries.

Considering that adult renal cell carcinoma – rare - acquired cystic disease associated had been only sporadically reported in few case reports as well as case series, it would be envisaged that only very few clinicians globally including Urologists, nephrologists, pathologists, radiologists, General Practitioners and other clinicians would be aware of the manifestation, diagnosis, treatment and outcome of this rare neoplasm. The ensuing article on adult renal cell carcinoma – rare - acquired cystic disease associated has been divided into two parts: [A] Overview which has discussed miscellaneous aspects of the tumour and [B] Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Studies.

Aim

To review and update the literature on adult renal cell carcinoma – rare - acquired cystic disease associated is the commonest RCC in patients who have ACD

Methods

Internet data bases were searched including: Google; Google Scholar; Yahoo and PUBMED. The search words that were used included: adult renal cell carcinoma – rare - acquired cystic disease. Thirty-four (34) references were identified which were used to write the article that has been divided into two parts: [A] Overview which has discussed miscellaneous aspects of the tumour and [B] Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Studies.

Results

[A] OVERVIEW

Definition / general statements [19]

- Acquired cystic disease associated adult renal cell carcinoma is stated to be a unique morphology of renal cell carcinoma (RCC) which arise within kidneys that have acquired cystic disease (ACD) due to end stage renal disease (ESRD), that is typified by microcystic / sieve-like, papillary and solid architecture, eosinophilic and clear cells and abundant calcium oxalate crystals [20]

It has been iterated that most common RCC in patients who have ACD, comprise 36% of all epithelial neoplasms that arise ESRD [20] [21]

Essential features [19]

It has been pointed out that adult renal cell carcinoma – rare - acquired cystic disease associated is the commonest RCC in patients who have ACD [21]

It has been iterated that adult renal cell carcinoma – rare - acquired cystic disease does contain abundant oxalate crystals

- With regards to morphology, it has been stated that the tumour consists of mixed solid, microcystic, papillary architecture with eosinophilic and clear cells
- It has also been iterated that adult renal cell carcinoma-acquired cystic tumour, generally portends an indolent biological behaviour, perhaps due to the early detection of the tumour.

Epidemiology [19]

- With regards to epidemiology, it has been stated that ACD does occur in 35% of long-term dialysis patients as well as and out of these, 6% do develop RCC

Sites

- The tumour has been documented to afflict the kidney [19]

Clinical features [19]

- The clinical manifestations of the tumour had been summated as follows: [19] pathologyoutlines.com
- The tumour often portends an indolent clinical biology behaviour, which had been suggested to be likely in part due to the early detection of the tumour with periodic radiology imaging assessment of patients who have ESRD [21]
- It has been iterated that that adult renal cell carcinoma – rare - acquired cystic disease tumours that exhibit sarcomatoid, rhabdoid or sometimes typical features could metastasize [20] [21]

Laboratory Investigations

Urine

Urinalysis, urine microscopy and urine cytology are urine tests that tend to be undertaken in patients who manifest with non-visible and visible haematuria associated with cystic disease of the kidney. The results of these tests could all be normal or there may be evidence of microscopic haematuria only. If there is evidence of urinary tract infection, the infection would be treated based upon the antibiotic sensitivity pattern of the cultured organism to help improve the general status of the individual patients. Urine cytology results would tend to be normal or demonstrate whether or not, there are abnormal urothelial cells to suggest urothelial carcinoma.

Haematology blood tests

Routine haematology blood tests including full blood count and INR as well as coagulation screen tend to be undertaken in the initial assessment of individuals who manifest with haematuria as well as who are taking aspirin and anticoagulant medications as part of their general assessment. If there is anaemia, it would be treated appropriately to improve the upon the general condition of the patient.

Biochemistry blood tests

CRP, serum urea and electrolytes, liver function tests, bone profile, and random blood glucose are routine tests that tend to be undertaken in the general assessment of patients who manifest with visible haematuria or are known to have chronic kidney disease. If the estimated glomerular filtration rate of a patient is reported to be lower than 30, contrast is not used in the radiology imaging scan of the patient so as not to induce any further possible damage to the kidneys and in this case, non-contrast ultrasound scan of the renal tract, abdomen and pelvis, or non-contrast computed tomography (CT) scan of the renal tract, abdomen and pelvis or non-contrast magnetic resonance imaging (MRI) scan of renal tract abdomen and pelvis is usually undertaken in the assessment.

Radiology Imaging

Ultrasound scan

- Ultrasound scan of renal tract, abdomen without contrast is the most common radiology imaging which tends to be undertaken and ultrasound scan-guided biopsy of any abnormal looking kidney and PIRADS 4 and 5 complex kidney lesions tend to be undertaken for histopathology and immunohistochemistry studies which would establish or negate presence of a kidney tumour and if there is presence of a kidney tumour, the general status of the patient would be assessed and the treatment options including partial nephrectomy, radical nephrectomy, cryotherapy of the tumour, radiofrequency ablation of the tumour, irreversible electroporation of the tumour, or selective renal artery angiography and super-selective embolization of the renal artery branch supplying the tumour could be undertaken based upon the recommendations and acceptance of the patient.
- Post treatment follow-up assessments of patients could be undertaken utilizing ultrasound scan of abdomen and pelvis, renal tract and chest x-rays in less resourced areas of the world to enable patients to pay for their regular assessments.

- Computed Tomography (CT) scan of renal tract, abdomen without contrast is the most common radiology imaging which tends to be undertaken and CT scan-guided biopsy of any abnormal looking kidney and PIRADS 4 and 5 complex kidney lesions tend to be undertaken for histopathology and immunohistochemistry studies which would establish or negate presence of a kidney tumour and if there is presence of a kidney tumour, the general status of the patient would be assessed and the treatment options including partial nephrectomy, radical nephrectomy, cryotherapy of the tumour, radiofrequency ablation of the tumour, irreversible electroporation of the tumour, or selective renal artery angiography and super-selective embolization of the renal artery branch supplying the tumour could be undertaken based upon the recommendations and acceptance of the patient.
- Post treatment follow-up assessments of patients could be undertaken utilizing CT scan of abdomen and pelvis, renal tract and chest.

Magnetic Resonance Imaging Scan

- Magnetic Resonance Imaging (MRI) scan of renal tract, abdomen without contrast is the most common radiology imaging which tends to be undertaken and MRI scan-guided biopsy of any abnormal looking kidney and PIRADS 4 and 5 complex kidney lesions tend to be undertaken for histopathology and immunohistochemistry studies which would establish or negate presence of a kidney tumour and if there is presence of a kidney tumour, the general status of the patient would be assessed and the treatment options including partial nephrectomy, radical nephrectomy, cryotherapy of the tumour, radiofrequency ablation of the tumour, irreversible electroporation of the tumour, or selective renal artery angiography and super-selective embolization of the renal artery branch supplying the tumour could be undertaken based upon the recommendations and acceptance of the patient.
- Post treatment follow-up assessments of patients could be undertaken utilizing MRI scan of abdomen and pelvis, renal tract and chest.

Positron Emission Tomography / Computed Tomography (PET/CT) scan

- PET/CT scan tends to be undertaken in some situations to ascertain in post-surgery follow-up assessments of patients to enable early recurrence of tumour.

Isotope Bone scan

- Isotope bone scan also tends to be undertaken in the follow-up assessment of patients who had undergone surgical treatment for kidney tumour to ascertain if they have developed bone metastasis when the present with bone pain.

Diagnosis

Diagnosis of kidney tumours in patients who have renal tumour tends to be established by:

- Pathology examination of radiology image-guided biopsy of the renal lesion.
- Pathology examination of radiology partial nephrectomy or radical nephrectomy specimen or excised specimen of the renal lesion.

Gross description

The macroscopy pathology examination features of the tumour had been summated as follows: [19]

- Gross examination of the kidney tumour does demonstrate a mass lesion in ACD background which usually measures 3 cm or less than 3 cm.
- It has been stated that gross examination of the kidney containing the tumour does tend show that the tumour is multifocal in about 50% of cases and bilateral in 25% of cases. [21]

Microscopic (histologic) description

The microscopy histopathology examination features of adult renal cell carcinoma – rare - acquired cystic disease had been summated as follows: [19]

- Microscopy histopathology examination of specimens of adult renal cell carcinoma – rare - acquired cystic disease does tend to demonstrate Cribriform / microcystic / sieve-like architecture of the kidney tumour
- Microscopy histopathology examination of specimens of adult renal cell carcinoma – rare - acquired cystic disease does tend to demonstrate abundant granular eosinophilic cytoplasm with prominent nucleoli within the tumour.
- Microscopy histopathology examination of specimens of adult renal cell carcinoma – rare - acquired cystic disease does tend to demonstrate Intra-tumoral calcium oxalate crystals which tend to be very common but the finding has also been stated not to be necessary for the establishment of the diagnosis. [22]
- Microscopy histopathology examination of specimens of adult renal cell carcinoma – rare - acquired cystic disease may demonstrate sometimes nodules arising from cyst walls or masses separated from cysts but not always [23]
- Microscopy histopathology examination of the kidney tumour may sometimes demonstrate prominent clear cell cytology

Cytology Description [19]

Cytology examination of specimens of adult renal cell carcinoma – rare - acquired cystic disease does tend to demonstrate moderately cellular, papillary clusters of polygonal to columnar cells with abundant eosinophilic granular cytoplasm, round and central nuclei, finely granular chromatin, prominent central grade 3 nucleoli [24]

Immunohistochemistry staining studies:

Positive stains [19]

- It has been iterated that specific immunohistochemistry staining profile of the tumour is not required in order to establish the diagnosis [23]
- It has also been iterated that immunohistochemistry staining studies of the does demonstrate positive staining of the tumour for the ensuing tumour markers:
  - CD10.
  - AE1/AE3, [25]
  - AMACR [21]

Negative stains

- It has been documented that immunohistochemistry staining studies of adult renal cell carcinoma – rare - acquired cystic disease does tend to demonstrate negative staining for ensuing tumour markers: [19]
  - EMA
  - CK7 but the tumour may be focally positively stained for CK7. [23]

Molecular / cytogenetics description

The molecular / cytogenetics study features of the tumour had been summated as follows: [] pathologyoutlines.com

- Comparative genomic microarray and FISH studies do demonstrate gains and losses of multiple chromosomes [23]
- Gains of sex chromosomes and gains of 3, 7, 16, 17 had been documented in these tumours. [21]
- High prevalence of gains of Y, 3 and 16 distinguishes from papillary RCC, which also has gains in chromosomes 7 and 17 in the tumour had been documented. [21]

Differential diagnoses

Some of the differential diagnoses of the tumour had been stated to include the following: [19]

- Clear cell renal cell carcinoma: it has been pointed out that both tumour entities may have clear cells and tubular architecture

- ACD RCC has regions of eosinophilic cells, papillary architecture, oxalate crystals as well as a background cystic renal parenchyma
- Papillary renal cell carcinoma: Both tumours may depict a papillary architecture and eosinophilic cells
  - ACD RCC has a typifying sieve-like architecture, and does contain oxalate crystals and a background cystic renal parenchyma
  - CK7 is usually negative in ACD RCC but tends to be positive in PRCC

[B] Miscellaneous Narrations and Discussions from Some Case Reports Case Series and Studies

Tickoo et al. [20] stated the following:

- Majority of renal cell carcinomas amounting up to 71% of renal cell neoplasms occurring in patients who have end-stage renal disease (ESRD), especially with acquired cystic disease of the kidney (ACDK), had been reported to be papillary renal cell carcinoma (RCC).
- Their initial experience with tumours in such a setting had suggested that many tumours were histologically difficult to classify into the known subtypes of RCC or they had features which were different from those in sporadically occurring RCCs.

Tickoo et al [20] undertook a study on 66 ESRD kidneys, 52 of which had shown features of ACDK) that had been excised because tumours were detected in them, and they found two major groups of RCC. Overall, there were 261 grossly identified tumours within these kidneys, and many additional tumours were identified upon microscopic histopathology evaluation in some of the tumours. Out of the two major groups of RCCs, one group of tumours consisted of tumours that simulated those tumours that are seen in sporadic settings (for example: clear-cell, papillary, and chromophobe RCC), and these formed the dominant mass in 12 tumours that amounted 18%, 10 tumours that amounted to 15%, and 5 tumours that amounted to 8% of the 66 kidneys, respectively. The other group of tumours consisted of two subtypes of RCC which appeared quite unique to ESRD. The more common tumour which they had designated as "acquired cystic disease-associated RCC" was noted as the dominant mass in 24 tumours that amounted to 36% of 66 of the kidneys, and it formed the most common type of tumour among the smaller nondominant masses, as well. It was typified by a typical microcystic architecture, eosinophilic cytoplasm with Fuhrman's grade 3 nuclei, and frequent association with intra-tumoral oxalate crystals. Furthermore, these tumours frequently, but usually focally, had exhibited papillary architecture, and clear cytoplasm. These tumours were noted to have occurred only in kidneys that were afflicted by ACDK, and not in non-cystic ESRD. The other category was "clear-cell papillary RCC of the end-stage kidneys," that was found present as the dominant mass in 15 tumours that amounted to 23% of the 66 kidneys and which had occurred in both the ACDK and non-cystic ESRD. These predominantly cystic tumours had exhibited prominent papillary architecture with purely clear-cell cytology. Immunohistochemistry staining studies in tumours that had histology that simulated the known subtypes of sporadic RCC had exhibited immune profiles that simulated the profiles which were reported in sporadically occurring tumours. The two subtypes of RCC unique to ESRD had distinctive immune profiles which supported their separate morphology subcategorization. Only the acquired cystic disease-associated RCC had demonstrated lymph node metastases in 2 cases and sarcomatoid features in 2 more cases. One of the latter 2 died with widespread metastatic disease within 34 months pursuant to undergoing nephrectomy. Thus, a broad spectrum of renal cell tumours, do exist in ESRD, only some of which mimic the sporadic RCCs. Tickoo et al. [20] made the ensuing concluding iteration:

- Acquired cystic disease-associated RCC is the commonest tumour subtype in ESRD, and biologically it does appear to be more aggressive in comparison with the other tumour subtypes in ESRD.
- Srigley et al. [23] made the ensuing iterations:
- The classification working group of the International Society of Urological Pathology consensus conference on renal neoplasia was in charge of making recommendations related to additions and changes to the current World Health Organization Classification of Renal Tumours (2004).
- Members of the group undertook an exhaustive literature review, assessed the results of the preconference survey and participated in the consensus conference discussion and polling activities.
- Upon the basis of the above inputs, there was consensus that 5 entities should be recognized as new distinct epithelial tumours within the classification system including: tubulocystic renal cell carcinoma (RCC), acquired cystic disease-associated RCC, clear cell (tubulo) papillary RCC, the MiT family translocation RCCs (in particular t(6;11) RCC), and hereditary leiomyomatosis RCC syndrome-associated RCC. Furthermore, there are 3 rare carcinomas which were regarded as emerging or provisional new entities including: thyroid-like follicular RCC; succinate dehydrogenase B deficiency-associated RCC; and ALK translocation RCC.
- Additional reports of these entities are necessitated in order to better understand the nature and biological behaviour of these highly unusual tumours.
- There were a number of new concepts or postulates which had suggested modifications to the existing World Health Organization 2004 categories. Within the clear cell RCC group, it was agreed upon that multi-cystic clear cell RCC should be best considered as a tumour of low malignant potential.
- There was consensus agreement that subtyping of papillary RCC is of value and that the oncocytic variant of papillary RCC should not be considered as a distinct entity.
- The hybrid oncocytic chromophobe tumour, which is an indolent tumour which occurs in 3 settings, namely Birt-Hogg-Dubé Syndrome, renal oncocytosis, and as a sporadic neoplasm, had been placed, for the time being, within the chromophobe RCC category.
- Recent advances that are related to collecting duct carcinoma, renal medullary carcinoma, and mucinous spindle cell and tubular RCC were elucidated.
- Outside of the epithelial category, advances in our understanding of angiomyolipoma, including the epithelioid and epithelial cystic variants, were considered.
- Furthermore, the apparent relationship between cystic nephroma and mixed epithelial and stromal tumour had been discussed, with the consensus opinion that these tumours form a spectrum of neoplasia.
- Finally, it was considered that synovial sarcoma should be removed from the mixed epithelial and mesenchymal category and placed within the sarcoma group.
- The new classification would be referred to as the International Society of Urological Pathology Vancouver Classification of Renal Neoplasia.

Rioux-Leclercq et al. [1] reported 2 cases of renal cell carcinoma which had arisen in acquired cystic disease of the kidney (ACDK) in patients who had end-stage renal disease undergoing haemodialysis for more than 5 years and provided a brief review of the complications of ACDK. In both cases, abundant calcium oxalate crystals identified within the

tumours. Histologically, one of the tumours was found to be a conventional (clear cell) renal cell carcinoma. The other tumour was a bilateral papillary renal cell carcinoma. Both tumours were histopathology examination graded as high-grade carcinomas which contained extensive oncocytic (acidophilic) features. Also identified within the kidneys were cysts with atypical papillary hyperplasia. The clinicopathology findings together with their review of the literature had indicated a relationship between tumour growth and calcium oxalate crystal deposition in patients who were undergoing haemodialysis with ACDK.

Kuroda et al. [26] reported a rare case of undescribed acquired cystic disease (ACD)-associated renal cell carcinoma (RCC) with sarcomatoid change. Kuroda et al. [26] reported a 78-year-old woman, who had been receiving haemodialysis for fourteen years at the time when she was found to have a renal tumour during her follow-up clinical and radiology imaging assessments of her kidney. Microscopy examination of the kidney specimen demonstrated, oncocytic cuboidal cells proliferated with tubular, cribriform or papillary growth patterns, and atypical columnar cells with abundant cytoplasm proliferated with papillary configuration. Oxalate crystal deposition was identified within the stroma and the tumour focally simulated translocation type (TFE3) RCC. Sarcomatous neoplastic cells were also identified during the pathology examination of the kidney tumour. The cytoplasm of the oncocytic as well as the sarcomatous neoplastic cells was diffusely positive for anti-mitochondrial antibody and the ultrastructural examination had demonstrated many mitochondria within the cytoplasm of oncocytic carcinoma cells and sarcomatous neoplastic cells. The loss of chromosomes 1p, 2q11-22, 9 and 14 was identified utilising comparative genomic hybridization analysis. Kuroda et al. [26] concluded that they had thus, reported a case of hitherto undescribed ACD-associated RCC intermingled with oncocytic cells, translocation type RCC-like area and sarcomatoid change and that their reported case was the sixth case of sarcomatoid RCC arising within end-stage kidney disease.

Sule et al. [22] stated the ensuing:

- The main complication of acquired cystic kidney disease (ACKD) is the frequent development of kidney tumours, including renal cell carcinoma (RCC).
- Intra-tumoral deposition of calcium oxalate (CaOx) is a distinct feature of ACKD-associated RCCs, however, several features of this type of RCC were not known.

Sule et al. [22] evaluated and compared the features of the 30 end-stage renal disease (ESRD)-associated RCCs which had been identified within a 13-year period, including eight with CaOx deposition. Sule et al. [22] evaluated and compared the pathology as well as the clinical features of CaOx positive (+) and negative (-) RCCs. The CaOx+ RCCs had shown higher tendency for bilaterality and multifocality. Seven tumours had depicted distinctive morphology features typified by tumour cells with ill-defined cell membrane, abundant granular eosinophilic cytoplasm, large nuclei, and prominent nucleoli. One tumour was of clear cell type. Irrespective of the histology type, all of the tumours had displayed a proximal tubular differentiation. No significant difference was identified for tumours' stage, proliferation, and apoptosis rate between the CaOx+ and CaOx- RCCs. CaOx+ RCCs accounted for a significant portion of all ESRD-associated RCCs. The majority of these RCCs had displayed a distinctive morphology profile. Sule et al. [22] concluded that proximal tubular cell differentiation in conjunction with ESRD-mediated high serum level might be pathogenetically important for the deposition of intra-tumoral and that these RCCs did appear to have a relatively good prognosis.

Dry et al. [27] Calcium oxalate crystals are common in renal disease; however, to our knowledge they have not been reported previously in renal cell carcinoma. Dry et al. [27] reported two patients who had papillary renal cell carcinoma and extensive calcium oxalate crystal deposition within the tumours. Both patients had end-stage renal disease and acquired renal cystic disease. Radiology imaging studies had demonstrated calcifications within one case. Histologically, both tumours were reported to have exhibited papillary features and had numerous calcium oxalate crystals within cystic spaces and papillae. Dry et al. [27] iterated that the presence of calcium oxalate crystals within these tumours was additional evidence that papillary renal cell carcinomas and acquired cysts might be related.

Bhanagar and Alexiev [28] stated that Clear-cell papillary renal-cell carcinoma (CCPC) and acquired cystic kidney disease-associated carcinoma (ACDAC) are neoplasms that are associated with distinct morphology characteristics which behave less aggressively in comparison with conventional renal-cell carcinomas. Bhanagar and Alexiev [28] selected End-stage kidney specimens from 61 patients which included 47 males and 14 females who had 109 renal-cell carcinomas. Papillary renal-cell carcinoma was the commonest malignancy which included 61 out of 109 cases, that amounted to 56%, followed by CCPC in 20 out of 109 cases, that amounted to 18% of the cases. The CCPC had depicted a papillary or tubular/solid architecture, clear cytoplasm, low nuclear grade, and a distinct immunohistochemical profile (RCC-, vimentin+, CK7+, p504S-). ACDAC displayed a variety of architectural patterns, eosinophilic cytoplasm, high nuclear grade, intra-tumoral calcium oxalate deposits, and an immunohistochemistry staining profile that was similar to type 2 papillary renal-cell carcinoma (RCC+, vimentin+, CK7-/+, p504S+). Less than 5% of tumours in 3 of 69 tumours of pathologically staged renal-cell carcinomas in end-stage kidneys had manifested with lymphogenous and/or hematogenous metastases.

Alaghehbandan et al. [29] stated the ensuing:

The World Health Organization (WHO) 2022 classification of urinary and male genital tumours (5th edition) had significantly improved their understanding of the morphology, immunohistochemistry, and molecular characteristics of kidney tumours. Alaghehbandan et al. [29] undertook a review which was aimed to outline the most important changes and diagnostic updates in the WHO 2022 classification of kidney tumours. Alaghehbandan et al. [29] reported the following:

- A major change in this edition is the grouping of kidney tumours into broader categories which include "clear cell renal tumours", "papillary renal tumours", "oncocytic and chromophobe renal tumours", "collecting duct tumours" as well as adding two categories of "other renal tumours" and "molecularly defined renal carcinomas".
- New entities included in the WHO 2022 classification are eosinophilic solid and cystic renal cell carcinoma (ESC RCC), anaplastic lymphoma kinase (ALK)-rearranged RCC and ELOC (formerly TCEB1)-mutated RCC. The category of "other renal tumours" that includes a group of diverse, unrelated renal tumours that do not fit into other categories.
- The group of "molecularly defined renal carcinomas" does reflect recent discoveries in the kidney tumour genomics.
- These molecularly-defined renal entities demonstrate a set of morphology characteristics that reflect genotype-phenotype relationships.
- Final diagnosis of such entities rests upon phenotypic and immunohistochemistry staining studies (IHC) correlation, that are usually associated with IHC surrogate makers that reflect specific genetic abnormalities.

Hes et al. [30] iterated the ensuing:

- The 5th edition of WHO classification of adult kidney tumours had introduced a couple of changes in existing, well-established entities, as well as some new distinct kidney tumours.
- Papillary renal cell carcinoma (RCC) is no longer divided into type 1 and type 2.
- Type 1 is now called “ classic” variant and type 2 doesn´t exist anymore.
- There were long discussions related to problematic type 2.
- According to WHO 2022 the correct name is papillary RCC (and subtype/variant should be mentioned in the description).
- Another important change came for clear cell papillary RCC.
- In view of the fact that there is no convincing evidence that genuine clear cell papillary RCC could produce recurrences or metastases, it is now referred to as clear cell papillary tumour.
- All previously reported aggressive cases are now regarded as misclassified clear cell RCC (mostly) or other entities.
- In less typical cases, genetic support of diagnosis with complex analysis of VHL gene should be added. New category “ other oncocytic tumours” emerged for tumours from grey zone between renal oncocytoma and chromophobe RCC.
- Term hybrid oncocytic tumour should be reserved for those with hereditary Birth-Hogg-Dubé syndrome. Emerging entities, like eosinophilic vacuolated tumour (EVT) and oncocytic low-grade tumour (LOT) are mentioned, however, more work is needed for better establishment of the criteria. There is a new category of “ molecularly defined renal carcinomas” where MITf translocation RCCs have been divided into TFE3 rearranged RCC with fusion partner dependent morphologic variability, and to TFEB rearranged RCC. In this group, indolent TFEB translocated RCCs are recognized, as well as potentially aggressive RCC with TFEB gene amplification.
- In WHO 2016, ALK rearranged RCC was regarded to be emerging entity. In WHO 2022 it is listed among “ molecularly defined RCC” as a distinct kidney tumour with broad morphologic spectrum dependent partly upon fusion partners. ELOC (TCEB1) mutated RCC is kidney tumour composed of clear cell elements and huge fibromyomatous stroma.
- Diagnostic approach should be complex with support of immunohistochemistry (including CK7) and molecular genetic approach. Nevertheless, there is overlap with MTOR pathway genes mutated RCC with fibromyomatous stroma. SMARCB1 deficient renal medullary carcinoma is high-grade invasive adenocarcinoma in patients with clinically proved sickle-cell trait and SMARCB1 deficiency.

Rizzo et al. [31] stated the following:

- The new WHO classification of urogenital tumours published in 2022, contains significant revisions made upon the previous 2016 version regarding Renal Cell Carcinoma (RCC).
- Whilst the commonest histotype does remain almost untouched, some of the main novelties concerns papillary RCC and oncocytic neoplasms.
- The main change is the introduction of a new category of molecularly-defined RCC, which includes the following tumours: TFE3-rearranged RCC, TFEB-rearranged, and TFEB-amplified RCC, FH-deficient RCC, SDH-deficient RCC, ALK-rearranged RCC, ELOC (formerly TCEB1)-mutated RCC, SMARCB1 (INI1)-deficient RCC.

Pezzicoli et al. [32] stated the following:

- Clear cell renal cell carcinoma (ccRCC) treatment had undergone three major paradigm shifts in recent years, first with the introduction of molecular targeted therapies, then with immune checkpoint inhibitors, and, more recently, with immune-based combinations.
- Nevertheless, up to date, molecular predictors of response to targeted agents had not been identified for ccRCC.
- The WHO 2022 classification of kidney tumours has introduced the molecularly defined RCC class, which is a first step in the direction of a better molecular profiling of RCC.

Pezzicoli et al. [32] reviewed the literature data related to known genomic alterations of clinical interest in ccRCC, which had discussed their prognostic and predictive role. In particular, they explored the role of VHL, mTOR, chromatin modulators, DNA repair genes, cyclin-dependent kinases, and tumour mutation burden. Pezzicoli et al. [32] iterated that RCC is a tumour whose pivotal genomic alterations have pleiotropic effects, and the interplay of these effects determines the tumour phenotype and its clinical and biological behaviour. Therefore, it is difficult to identify a single genomic predictive factor, however, it is more likely to identify a signature of gene alterations that could impact upon the prognosis and response to specific treatment. Pezzicoli et al. [32] also stated that in order to accomplish this task, the interpolation of large amounts of clinical and genomic data is required. However, genomic profiling has the potential to change real-world clinical practice settings.

Bretan PN Jr et al. [10] reported three male patients who had end-stage renal disease on chronic haemodialysis who had manifested with visible haematuria and who were subsequently found to have acquired renal cyst disease and progressive bilateral renal cell carcinoma. Bretan PN Jr et al. [10] iterated the ensuing:

- There were at the time of publication of their article in 1986, more than 84 similar cases in the literature, but the precise roles that renal failure and haemodialysis play in the development of renal cysts and renal neoplasms was not clear.
- The high incidence of acquired renal cyst disease of 45% and the development of renal tumours in 9% of cases, with a 5% to 7% metastatic rate in patients with end-stage renal failure clearly underscores the need for more intense radiology image monitoring.

Cossu-Rocca et al. [33] iterated the following:

- End-stage renal disease is associated with an increased incidence of renal cell neoplasms. Among these, recent studies had demonstrated tumours associated with unusual histology patterns which do not fit into the categories recognized in the current classification system at the time of publication of their article in 2006.
- These tumours often had occurred in kidneys with acquired cystic disease and were comprised mainly of large eosinophilic cells which were arranged in solid, cribriform, acinar, or papillary patterns. They also contain deposits of calcium oxalate crystals.

Cossu-Rocca et al. [33] investigated three eosinophilic epithelial tumours arising in kidneys that contained acquired cystic disease from three patients. Each of the tumours was reported to be composed of large eosinophilic cells arranged in solid, acinar, or tubulocystic architecture. Deposits of calcium oxalate crystals were found present within each tumour. Hale's colloidal stain had shown a positive cytoplasmic reaction in one of the neoplasms. Immunohistochemistry staining studies displayed positive results for CD10 (3/3), AE1/AE3 (3/3), alpha-methylacyl-CoA racemase (2/3), CAM5.2 (2/3), and vimentin (1/3). Reactions for epithelial membrane antigen, cytokeratin 7, and high

molecular weight cytokeratin (34betaE12) were negative. Fluorescence in situ hybridization analysis had demonstrated no losses or gains of chromosomes 1, 2, 6, 10, or 17 in one tumour. There were gains of chromosomes 1, 2, and 6 in two tumours. One of these tumours also had depicted gains of chromosome 10. Eosinophilic renal cell tumours associated with acquired cystic disease had immunophenotypes and genetic profiles distinct from the renal cell neoplasms recognized in the classification of renal cell neoplasia, at the time of publication of their article which in their opinion should be considered as a distinct clinicopathologic entity in the spectrum of renal cell neoplasia.

Carnahan et al. [] stated the ensuing:

- Acquired cystic kidney disease (ACKD) is commonly encountered in patients who have end-stage renal disease (ESRD), and patients who have ACKD do have an increased risk for the development of renal cell carcinoma (RCC).
- Acquired cystic disease-associated RCC (ACD-RCC) was added to the 2016 World Health Organization Classification.

Carnahan et al. [34] described the radiology imaging features of ACD-RCC, which had not been well reported previously. Carnahan et al. [34] undertook a retrospective review of patients who had ACKD who had undergone total nephrectomy for concern of a renal mass between 2016 and 2021 and this yielded 122 nephrectomies in 107 patients. Carnahan et al. [34] searched the pathology reports of the cases for type and subtype of mass. Carnahan et al. [34] iterated that in ACD-RCC subtypes, radiology imaging studies, were evaluated for modality and contrast enhancement (CE). Carnahan et al. [34] also reported that imaging findings were assessed and these included cystic/solid nature, unenhanced CT (NECT) attenuation, enhancement characteristics [non-enhancing (< 10 HU difference), equivocal (10-20 HU), enhancing (> 20 HU)], subjective MRI enhancement, T1 and T2 signal intensity, restricted diffusion, ultrasound (US) echogenicity, and subjective CEUS enhancement.

Carnahan et al. [34] summarized the results as follows:

- They had identified 148 masses, 122 (82%) of which were found to be malignant and 26 (18%) benign.
- The three commonest tumours were clear cell RCC which comprised of 47 cases, papillary RCC which comprised of 35 cases, and ACD-RCC which comprised of 21 cases.
- Out of the 21 cases of ACD-RCC, 16 had preoperative radiology imaging including: CT scan (15 cases: 6 patients underwent non-contrast computed tomography [NECT) scan only, 2 had contrast-enhanced (CECT) scan only, 7 patients had combined NECT and CECT), Magnetic Resonance Imaging [MRI] scan in 4 cases, Contrast-enhanced ultrasound scan [CEUS] in 5 cases.
- Ten of these tumours were solid/mostly solid and 6 mixed cystic/solid.
- Upon NECT, the average attenuation was 35 HU and the attenuation had ranged between 13 and 52. Of those with multiphasic CTs, 1 was non-enhancing, 3 were equivocal, and 3 enhanced. All 3 masses that were imaged utilizing CE-MRI had shown enhancement.
- All 4 tumours that were evaluated by MRI had demonstrated T2 hypointensity and restricted diffusion.
- All five masses enhanced on CEUS.

Carnahan et al. [34] made the ensuing conclusions:

- ACD-RCC subtype was the third commonest renal neoplasm in ACKD patients.
- Their findings had found that no single radiology imaging feature is pathognomonic for ACD-RCC.
- Nevertheless, ACD-RCCs are typically solid masses with most of the tumours demonstrating equivocal or mild enhancement on CT.
- T2 hypointensity and restricted diffusion were the commonest MRI scan features.

Conclusions

- A spectrum of renal cell tumours does exist in end stage renal disease (ESRD), and some of these tumours simulate the sporadic renal cell carcinomas (RCCs).
- Acquired cystic disease-associated RCC is the most common tumour subtype in ESRD, and biologically it does appear to be more aggressive than the other tumour subtypes in ESRD.
- Clinicians need to be aware that cystic changes in kidneys that occur following medium-term to long-term dialysis may be ensued by the subsequent development of kidney tumours and hence a high index of suspicion is required to establish early diagnosis of these tumours.
- Other treatment options that need to be considered in the management of some acquired cystic disease kidney tumours include: (a) Radiology-image-guided cryotherapy of the kidney tumour; radiology-image-guided radiofrequency ablation of the tumour; radiology-image-guided irreversible electroporation of the tumour, selective renal artery angiography and super-selective embolization of the tumour possibly in combination with immunotherapy.

Conflict of Interest – Nil

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